PHYSIOLOGICAL ASPECTS OF THE USE OF HYPOTHERMIA IN SPACE MEDICINE

P. V. Vasil'yev and G. D. Glod

The problem of controlled modification of reactivity of the living organism /443
by artificial hypothermia has long attracted the attention of investigators. The first accounts of the effective use of hypothermia in medical practice were given near the middle of last century [4, 21, 32]. However, until recently it could not be regarded as finally solved. Many theoretical and practical aspects of artificial hypothermia of the warm-blooded organism remained debatable.

Considerable advances in the field of study of pathophysiology of states with a reduced body temperature were achieved by the study of cooling and freezing [1, 6, 20], and also of the seasonal hibernation and anabiosis [2, 12, 17].

The most active period of study of the pathophysiology of artificial hypothermia of animals and man have been the last few decades [28, 29, 39, 43, 44, 47].

Many investigators have shown conclusively that artificial hypothermia is an effective means of treatment of anoxia and shock. Deep hypothermia has proved of great promise for prolonging the period of reversible changes during clinical death.

Because of the practical needs of anesthesiology and surgery, many investigations have been directed toward the study of the deepest possible reversible hypothermia for comparatively short periods.

The problem of prolonged hypothermia, which was widely studied in the 1950's [33-35, 42, 45], at present has few investigators. However, statements continue to appear in the literature on the great practical value of moderate prolonged hypothermia with complete preservation of vital activity of the organism. The suggestion has been made that hypothermia is potentially useful in space research [8, 17, 19, 27, 32, 41].

Experimental investigations have demonstrated an increase in the resistance of the artificially hypothermic organism to influences such as ionizing radiation and overloading [3, 5, 9-11, 13, 25, 26, 30, 46]. In addition, artificial hypothermia or artificial hibernation may be very convenient for the transportation of biological objects on board the spacecraft.

The methods of producing artificial hypothermia widely used in clinical /444
practice are cumbersome and technically difficult, and for that reason they are unsuitable for space research. Comparison of data in the literature on methods of moderate hypothermia does not permit preference being attached to any one of them, because of the largely contradictory opinions expressed. The main disagreements are concerned with the desirability and depth of hypothermia, the

method of cooling and, above all, the method of preventing excessive reflex reactions of the organism preventing the development of hypothermia.

Nowadays most authors use a combination of pharmacological blocking and cooling. However, the composition of "lytic mixtures" is not finally settled, and some investigators do not recommend their use at all, for they prevent operation of physiological control mechanisms during the period of recovery of functions on reheating.

The description of the character of the pathophysiological changes is extremely variegated for different authors frequently cite results obtained by different methods of artificial hypothermia. The most careful study has been made of the central nervous system and circulatory organs. Much less attention has been devoted to changes in respiration. This is because with the very first studies, marked disturbances of external respiration were established. Without going more deeply into their study, investigators followed the most logical paths from the point of view of clinical practice. To prevent possible respiratory anoxia, it became the common practice to use compensated, and later artificial, respiration against a background of deep curarization, more especially because this also solved a second, no less important problem, the prevention of reflex shivering. Naturally we can discuss a method of artificial hypothermia capable of use under space flight conditions on an actual basis only if it responds to a number of essential conditions. One of the most important of these is the following: the safety and reliability of the method, which is able to produce prolonged and easily controlled reversible hypothermia with a considerable decrease in reactivity of the organism. Obviously elements of the method such as artificial respiration and, in particular, the artificial circulation are ruled out. It thus follows that investigators are confronted by the problem of developing new methods of induction of moderate hypothermia responding most completely to the demands presented. Most attention must be paid to the more complete study of safety limits of the depth and duration of artificial hypothermia with maintenance of spontaneous respiration and circulation. Some attempts at solving these problems have been made by the present authors in experiments on albino rats and dogs. /445

Under standard conditions of external air cooling, various methods for preventing reflex reactions of the organism to the action of cold were tested. Different combinations of a "lytic mixture," short-action barbiturates, urethane anesthesia, relaxants, and a modified gaseous environment (hypercapnia and hypoxia) were used. Attention was concentrated on the study of the functions of gas exchange, respiration and the circulation.

The investigations revealed considerable differences in the course of hypothermia depending on the method used. Not one of the combinations of the substances mentioned completely prevented undesirable symptoms of stress on mechanisms of physiological compensation in the first stages of hypothermia. In all the experiments the first general adaptive response of the animal (as described by I.R. Petrov) was clearly observed, in the form of quickening of the heart rate, quickening and strengthening of respiration, some increase in the oxygen demand, muscular tremor, and so on. However, the severity and duration of this phase of hypothermia were due to the methods used to block reflex activity, and they enabled a comparative analysis to be made of the efficacy of

these methods. In experiments on rats, for instance, the best method of blocking thermoregulatory mechanisms during cooling was found to be an environment with a gradually increasing level of hypercapnia and hypoxia [8]. The first general adaptive reaction of the animal under these conditions was short in duration and ill defined. Besides the subsequent deep depression of all the principal vitally important functions of the organism, the ability for hypothermia to undergo rapid reversal persisted for a long time. Compared with other methods studied, this gave the highest oxygen level in the arterial blood, indicating not only the efficiency of external respiration, but also the more optimal conditions of maintenance of homeostasis. The enzyme systems of tissue respiration (succinate dehydrogenase and cytochrome oxidase of the liver) showed high resistance to hypothermia, and their activity remained unchanged when the body temperature of the animals had fallen to 20°. Moreover, the liver succinate dehydrogenase activity corresponded to the changed temperature of the tissue environment. For example, in rats cooled to 20° the oxygen demand was about one-fifth of its initial level, and the succinate dehydrogenase activity was lowered on the average of one-quarter. Having regard to the high resistance of tissue respiration mechanism to hypothermia, we were justified in assuming that during artificial hypothermia with maintenance of natural respiration, pathophysiological disturbances arise as a result of disturbances of functions of the organs supplying oxygen to the tissues.

The high resistance of albino rats, cooled under conditions of gradually increasing hypercapnia and hypoxia, to the action of prolonged radial acceleration, to hypoxic hypoxia, and to a high degree of rarefaction of the atmosphere (experiments carred out jointly with V.S. Oganov and N.N. Timofeyev) demonstrated the efficacy of the condition obtained. /446

Hypothermia produced by cooling with other methods for preventing reflex reactions greatly reduced the resistance of animals to overloading.

In experiments on dogs, the best method of preventing excessive reflex responses interfering with the development of hypothermia was by means of a neurovegetative block by "lytic mixture" (chlorpromazine 5 mg/kg, pipolphen 5 mg/kg, trimeperidine 1 mg/kg, and methyldiazine 0.5 mg/kg), combined with short-action barbiturate and controlled carbon dioxide anesthesia. The physiological indices studied showed considerable variation, but their degree differed from those in experiments using hypothermia under urethane anesthesia (Table 1).

The minute volume of respiration and the respiratory quotient, for instance, remained at a higher level whereas the oxygen consumption was lower. The function of the circulatory organs was inhibited much more deeply; the minute volume of the heart and the mean arterial blood pressure fell more than during urethane anesthesia, but the tissue oxygen supply was disturbed to a lesser degree. Despite the marked decrease in oxygen capacity of the blood because of "chlorpromazine" hydremia, the utilization of hemoglobin was more complete and the arterio-venous oxygen difference showed a much smaller change. All this indicated a less severe disturbance of homeostasis in the animals after blocking of thermoregulatory mechanisms by the "lytic mixture" and short-action barbiturates and, consequently, more favorable conditions for hypothermia to run its course than in the case of cooling during urethane anesthesia.

TABLE 1. Results of Comparison of Some Physiological Indices During Artificial Hypothermia in Dogs

Indices	Methods of blocking reactions to cooling			
	Lytic mixture and hexobarbital (50 mg/kg)		Urethane anesthesia (2.0 g/kg)	
	32–30°	27–25°	32–30°	27–25°
Minute volume of respiration, liters	1,1 * ±0,23	0,81±0,14	1,08±0,22	0,72±0,17
O_2 consumption, ml/kg/min	5,0±0,79	2,0±0,53	6,09±0,56	5,52±1,96
Respiratory quotient	0,53±0,02	0,53±0,03	0,52±0,04	0,46±0,04
Hematocrit index	30,1±3,32	34,4±2,7	69,3±4,83	75,5±6,06
O_2 concentration in arterial blood, v%	15,58±1,34	13,85±0,73	24,32±0,92	23,12±0,79
Arteriovenous differences in O_2, v%	6,16±0,17	6,11±0,82	4,62±1,08	4,52±1,47
Minute volume of heart, liters	0,58±0,089	0,38±0,089	0,75±0,134	0,91±0,114
Heart rate, % of initial	70,6±3,27	43,6±2,16	102,1±8,54	61,0±4,59

*Mean value ± mean error.
Commas represent decimal points.

The efficacy of the use of hypercapnia has been demonstrated clearly during cooling of rodents [14, 16, 24, 36]. Only occasional successful results of experiments on other species of animals have been described [25, 40]. In this connection our experiments on dogs were exploratory in character. The degree of hypercapnia varied from 5 to 60%, and various combinations of hypercapnia with the "lytic mixture" and short-action barbiturates were used; from the results of these experiments, the use of carbon dioxide anesthesia for blocking thermoregulation in dogs can be regarded as effective. Inhalation of hypercapnic gas mixtures (30-40% CO_2) made it possible to reduce the dose of barbiturates substantially (to 20-30 mg/kg), while maintaining an adequate depth of anesthesia. The advantages of inhalation anesthesia were preserved, and the /447
animals reacted precisely to changes in carbon dioxide concentration in the inhaled gas mixture, so that the process of hypothermia could be actively modified at any stage. The temperature limits for cessation of activity of the respiratory center were unchanged, but the volume of the pulmonary ventilation

remained higher throughout the experiment. Hypercapnia had a very favorable effect during recovery from hypothermia. Inhalation of a gas mixture containing 5-15% CO_2 blocked the developing motor excitation and the muscular tremor and thus facilitated the more economic utilization of energy resources in the body during restoration of the normal rhythm of vital activity.

Investigation of the mechanisms of disturbance of respiration in dogs in a state of artificial hypothermia showed that, just as in experiments on rats, the processes of tissue respiration showed high resistance to the action of cold and remained capable of utilizing oxygen at near-background level.

The duration of reversible hypothermia in our experimental conditions varied from a few hours to one day. The temperature limits of stabilization of artificial hypothermia were small and differed both from the comparative physiological standpoint and in animals of the same species. Optimal levels of the rectal temperature at which hypothermia could be prolonged were 18-20° for rats and 23-25° for dogs, isothermia being maintained with an external environmental temperature of 15-18°. Cooling the animals below these temperature limits led to disturbance of the mechanisms of physiological regulation, one of the first manifestations of which was disturbance of the rhythm, followed by cessation of spontaneous respiration, after which all subsequent disturbances in the body developed rapidly. The symptom-complex of disturbance of physiological regulation as a rule developed within a few minutes and recovery from hypothermia was possible only if rapid and energetic measures were taken. /448

The production of artificial reversible hypothermia with considerable depression of the vital functions yet with essential preservation of homeostasis is a matter of considerable difficulty. Not one of the known techniques can satisfy the demand which must be presented if the use of hypothermia under the conditions of long-term space flights can be met in the future. Moreover, it would obviously be unjustified to attempt to develop a universal method applicable to all biological objects without regard to their level of physiological organization.

It is difficult to judge the effectiveness of the state of artificial hypothermia obtained by examination of data such as the body temperature, the degree of lowering of the intensity of metabolic processes, and other physiological indices recorded in hypothermic animals. Under these circumstances the characteristics of development of hypothermia are very important, especially the degree of manifestation of its first (compensatory) phase, resulting from the use of the method of blocking reflex reactions to cooling.

Data in the literature and results of our own experiments can thus do no more than indicate some pathways for development of methods of artificial hypothermia for use in rats and dogs. The final solution of the problem requires extensive experimental research. Together with problems concerned with the development of methods for blocking thermoregulatory mechanisms, considerable attention must be paid to the investigation of the possibility of automation of the processes used in producing artificial hypothermia, to investigation of control over the basic physiological functions, of prolonged maintenance of the state of hypothermia and recovery from it. The investigations of Ye. V. Maystrakh and co-workers [14] and of others are of considerable interest in this respect.

The practical use of artificial hypothermia during space flights will evidently be for several purposes. The most important of these are as follows: /449 transportation of biological objects during flights of long duration, and their protection against the action of extreme factors (anoxia, radiation injury, etc.). The possibility is not ruled out that in future such a method of biological protection may also be used by the members of the spacecraft crew during long flights in various emergency situations calling for strict economy in the use of oxygen, water and food products. A solution to the problem may be found by developing a method of controllable superficial hypothermia of the "artificial hibernation" type. The energy gained in this manner may be much greater, for as numberous investigations by other workers have shown, the safe duration of artificial hibernation is many times greater than the possible duration of reversible artificial hypothermia. Should the need for the state of depressed vital activity be dictated by a single purpose--economy in oxygen and food, this will be the more promising method.

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